II. REMARKS

The Office Action dated October 28, 2008, has been received and carefully noted. The amendments made herein and the following remarks are submitted as a full and complete response thereto.

Claims 1-9 are pending in this application. Claims 2, 5, and 6 are withdrawn.

By this Amendment, claims 1 and 9 are amended. Applicants submit that support for the amendments can be found in the specification and the claims as originally filed. Applicants submit that no new matter is added and respectfully request reconsideration and withdrawal of the pending rejections.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 3, 4, and 7-9 are rejected under 35 U.S.C. § 112, first paragraph, for the asserted lack of enablement. This rejection is traversed.

Applicants respectfully disagree with the Examiner's assertion that the specification provides insufficient written description for the salts, "due to lacking chemical structural information for what they are and because chemical salts are highly variant and encompass a myriad of possibilities." Applicants submit that one of ordinary skill in the art would understand what is meant by a "salt" and that there is sufficient written description. Applicants submit that one of ordinary skill in the art would understand that the term "salts thereof" refers to pharmaceutically acceptable salts, as the claim is directed to a method of treatment to a subject. Further, Applicants submit that salts or pharmaceutically acceptable salts are often recited in claims and well understood by those skilled in the art.

Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 3, 4, and 7-9 under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 102(b)

Claims 1, 3, 4, 7 and 8 are rejected under 35 U.S.C. §102(b) as being anticipated by Armour et al. (*Arthritis and Rheumatism*, 2001, 44(9), pages 2185-2192, hereinafter

"Armour"). The Examiner asserts that Couchman et al. (Agents and Actions, 1986, 19(1/2), pages 116-122, hereinafter "Couchman") provides evidence of inherency of the function or mechanism of action of the treatment disclosed by Armour. Applicants traverse the rejection.

Present claim 1 is directed to a "method of treating degeneration of the cartilaginoid matrix comprising administering to a subject in need thereof an effective amount of one or more compounds" having formula (I). Claims 3, 4, 7, and 8 depend from independent claim 1.

Before addressing the present rejection, Applicants submit the following comments. Applicants submit that at the time of filing of the present application, it was well known that the drugs for treatment of arthritis were divided in two groups: (1) those providing symptomatic relief of pain while not arresting the progression of the disease, and (2) those arresting or slowing the progression of structural damage in joints, or disease-modifying agents. Applicants submit that it is clear that the two classes of drugs, while both effective for use in arthritis patients, are well differentiated in their pharmacological activity and mechanism of action. Applicants submit that the need to have drugs which are able to act on the progression of disease instead of symptoms was well recognized, as shown, for example, in the following enclosed publication: Arthritis & Rheumatism Vol. 43, No.9, September 2000, pp.1905-1915: "Recommendations for the medical management of osteoarthritis of the hip and knee" of American College of Rheumatology Subcommittee on Osteoarthritis Guidelines.

Applicants submit that on pp. 1907-1908 of the enclosed reference, the pharmacologic therapy for osteoarthritis is reported. The discussed therapy is based on NSAIDs and analgesics for the relief of pain. Applicants submit that it is clear that those drugs aim at obtaining symptomatic relief. Applicants note that on page 1912, which is in a chapter entitled "Agents under investigation," the Authors state: "The 1995 ACR recommendation briefly mentioned preliminary studies of disease modifying OA drugs (DMOADs), drugs whose action is not aimed principally at the control of symptoms, but

instead at the prevention of structural damage in normal joints at risk of development of OA, or at the progression of structural damage in joints already affected by OA."

Applicants submit that Armour does not disclose the presently claimed invention. In addition to our previously presented arguments, Applicants submit the following comments. Applicants disagree with the Examiner's assertion that because Armour discloses that "HCT1026 may be of clinical value in the prevention and treatment of inflammatory diseases such as rheumatoid arthritis" (see abstract), Armour inherently discloses a "method of reducing degeneration of the cartilaginoid matrix," which is a symptom seen in arthritis. Applicants submit that degeneration of the cartilaginoid matrix does not only occur in arthritis patients. In other words, Applicants submit that a subject could have degeneration of the cartilaginoid matrix but not have arthritis. For example, Applicants submit a website page excerpt from Medline Plus, which lists a number of non-arthritis conditions which are characterized by injury, inflammation, or damage to the cartilage (http://www.nlm.nih.gov/medlineplus/cartilagedisorders.html).

Applicants further submit that Perricone v. Medicis Pharmaceutical Corp., 432 F.3d 1368 (Fed. Cir. 2005), is relevant to the present application.

In Perricone, the Court of Appeals for the Federal Circuit ("the Federal Circuit") addressed the issue of anticipation by inherency and method of use claims. In particular, the Federal Circuit addressed the patentability of claims over a prior art reference, U.S. Patent No. 4,981,845 (the Pereira reference). Among the asserted independent claims of the patents at issue was a claim directed to a "method for treating skin sunburn" and a claim directed to a "method for preventing sunburn damage." The Pereira reference "teaches a cosmetic composition for topical application and discloses various ingredients in that composition, including skin benefit ingredients, emollients, emulsifiers, and thickeners." Id. at 1376. The Pereira reference also identified the compositions as being "suitable for topical application to the skin or hair." Id. However, the Pereira reference did not disclose the treatment of skin sunburn.

The Federal Circuit found that the claims directed to the treatment of skin sunburn were not anticipated by the Pereira reference. The Federal Circuit did

acknowledge that "[t]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's function, does not render the old composition patentably new to the discoverer." Id. at 1377 (quoting Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347 (Fed. Cir. 1999)). The Federal Circuit also found that the Pereira reference did anticipate claims directed to the method of preventing sunburn damage. However, the Court found that the method for treating sunburn was not anticipated, because the method of treating sunburn was not inherent in the Pereira reference.

The Federal Circuit rejected arguments that the cited reference teaches a composition that inherently functions in the claimed manner when topically applied to the skin. Rather, the Federal Circuit asserted:

> "The issue is not, as the dissent and district court imply, whether Pereira's lotion if applied to skin sunburn would inherently treat that damage, but whether Pereira discloses the application of its composition to skin sunburn. It does not... New uses of old products or processes are indeed patentable subject matter." Id. at 1378.

The Federal Circuit continued:

> "[The claim directed to the treating skin sunburn] recites a new use of the composition disclosed by Pereira, i.e., the treatment of skin sunburn. The district court's inherent anticipation analysis for this claim contains a flaw. The disclosed use of Pereira's lotion, i.e., topical application, does not suggest application of Pereira's lotion to skin sunburn. In other words, the district court's inherency analysis goes astray because it assumes what Pereira neither disclosed nor rendered inherent. Because Pereira does not disclose topical application *to skin sunburn*, this court reverses the district court's holding that Pereira anticipates claims 1-4 and 7 of the '693 patent." Id. at 1378-1379.

Applicants submit that the holding in Perricone v. Medicis Pharmaceutical Corp. is relevant to the present application. Applicants submit that, like in Perricone, the applied reference (in this case, Armour) does not teach the use of the disclosed compound for treatment of the claimed condition. Applicants submit that that Armour merely discloses that HCT1026 can be effective for joint inflammation and systemic

bone loss, and, based on the teachings of Armour, one of ordinary skill in the art would not know that HCT1026 could be effective in also treating degeneration of the cartilaginoid matrix, which is a condition characterized by an entirely different mechanism of action, involving distinctly different parts of the body. For example, as argued previously, degeneration of the cartilaginoid matrix involves the cartilage, whereas Armour is directed to bones and joints.

Applicants also submit that, similar to what the Federal Circuit stated in Perricone, the issue is not whether HCT1026 and related compounds, ***if*** administered to a subject experiencing degeneration of the cartilaginoid matrix, would inherently treat this condition. Rather, the issue is whether the prior art reference, Armour, ***discloses*** the use of HCT1026 and related compounds to treat the claimed condition. Applicants submit that since Armour does not, the rejection over Armour is improper.

Further, Applicants note the Examiner's assertion that "Armour et al. discloses HCT 1026 or flurbiprofen nitroxybutylester..... administered in vivo using a mouse model of ovariectomy-induced bone loss ..... a model that is a subject with arthritis." Applicants submit that the Examiner's assertion is without foundation, as said model is not a model of arthritis (see "Animals" under "Material and methods"). Rather, Applicants submit that the aim of the study was to examine the effect of HCT 1026 on bone metabolism using mice subjected to ovariectomy to induce bone loss. Applicants submit that the finding of the study was that HCT 1026 protects against bone loss. Applicants submit that none of the data reported in the study refers to subjects with degeneration of the cartilaginoid matrix.

Applicants submit the following comments regarding Couchman. The Examiner cites Couchman in order to demonstrate that it was known that NSAIDS reduced cartilage degradation. Applicants submit that the *in vitro* study in Couchman uses models of synovial tissue which comprise a number of cell populations other than chondrocytes. Applicants submit that the results reported therein are controversial, as they suggest that NSAIDs inhibit production chondrocyte stimulating factors but they do not effect preformed chondrocyte stimulating factors. Applicants note that the article is

from 1986, and it is not representative of the knowledge at the time of filing of the present application.

Applicants note that the effect of NSAIDS on cartilage was not completely clear at the time of filing of the present application and is not completely clear today. However, Applicants submit that the prevailing opinion is that NSAIDS have a negative effect on cartilage. See, for example, Mastbergen et al., Rheumatology, 2006; 45:405-413 (enclosed). Mastbergen et al. is a recently published article, but it refers to and discusses publications from 1986 to 2002, which Applicants submit gives a picture of the state of the art at the filing date of the present application. Applicants note that Mastbergen et al. discloses the following

> "In addition, beneficial effects of NSAIDs on inflammation mask possible direct adverse effects on cartilage. Direct effects of NSAIDs on cartilage may be important specifically in prolonged treatment of joint disease in which inflammation is only mild and secondary, as in OA. Data on direct effects of conventional NSAIDs on cartilage are numerous, but results are far from conclusive [8, 9]. Two frequently used NSAIDs that have been studied regarding their direct effects on cartilage are naproxen and indomethacin. Studies on the influence of naproxen show conflicting results; there are signs that naproxen suppresses cartilage proteoglycan synthesis in vitro [9, 10], but other studies show suppression of proteoglycan degradation [11, 12]. Indomethacin shows principally negative effects on the biochemical parameters of cartilage in vitro [9, 10] and animal studies [13, 14], but there are also studies that did not find any effect of indomethacin on cartilage [15, 16]"

(page 405).

Applicants further note Mihara et al., OsteoArthritis and Cartilage, 2007, 15:543-549 (enclosed). Mihara et al. states the following:

> "In contrast, in the LOX [loxoprofen] group, the cartilage degeneration was augmented compared with the control group. And, this exacerbated cartilage degeneration induced by LOX was reversed by the concomitant use of SVE [a high molecular weight hyaluronic acid]"

(see "Results" in Summary, page 543). In addition, Mihara et al. discloses:

> "Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of OA patients. Although NSAIDs are useful for pain management, there are many reports describing the possibility of accelerated disease progression... Huskisson et al. reported that indomethacin increased the rate of radiological deterioration of joint space in patients with OA of the knee compared with placebo... In another paper, Reijman reported that long-term use of diclofenac might induce accelerated progression of hip and knee OA in the Rotterdam study using 1695 patients..."

Therefore, Applicants submit that, at the time of filing of the present application, there was evidence that NSAIDs were deleterious to cartilage.

As Armour et al. does not disclose each and every element of the presently claimed invention, Applicants respectfully submit that Armour et al. does not anticipate the presently claimed invention. Accordingly, for at least the above reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 3, 4, and 7-8 under 35 U.S.C. § 102(b) as being anticipated by Armour et al.

Rejection under 35 U.S.C. 103(a)

Claims 1 and 9 are rejected under 35 U.S.C. §103(a) as being unpatentable over Armour, in view of El-Gabalawy et al. (*Arthritis Res.* 2002, 4 (suppl 3) pages S297-S301, hereinafter "El-Gabalawy"). The Examiner again cites Couchman for providing evidence of inherency of the function or mechanism of action of the treatment disclosed by Armour.

Present claim 1 has been discussed above. Claim 9 depends from independent claim 1.

Armour and its deficiencies have been discussed above. Applicants submit that El-Gabalawy generally discloses therapies for rheumatoid arthritis.

Applicants submit that, as discussed above, Armour does not teach or make obvious the presently claimed method, as discussed above. Applicants submit that El-Gabalawy does not fulfill the deficiencies of Armour, as El-Gabalawy does not teach or suggest the use of the claimed compounds to treat degeneration of the cartilaginoid matrix.

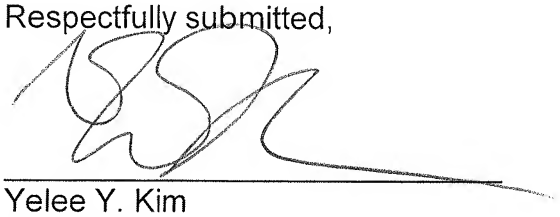
For at least the above reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1 and 9 under 35 U.S.C. § 103(a) over Armour and El-Gabalawy.

III. CONCLUSION

Applicants respectfully submit that this application is in condition for allowance and such action is earnestly solicited. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

In the event this paper is not considered to be timely filed, Applicant hereby petitions for an appropriate extension of time. The fee for this extension may be charged to our Deposit Account No. 01-2300, referring to Attorney Docket No. **026220-00055**. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300, referencing Attorney Docket No. **026220-00055**.

Respectfully submitted,



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Enclosures: References (4)